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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,992	ASHKENAZI, ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2004 has been entered.

In the response filed on 12/14/2004, several claims were cancelled (claims 39-41) and several claims were amended (claims 42-46 & 50). Claims 42-46 and 49-51 are pending and under consideration in the instant application. It is noted that the instant action could be made final as the response does not raise any new issues or make new arguments. The action has not been made final in order to allow applicants a chance to file their proposed opinion declaration concerning the proposed utilities for the PRO302 protein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 42-46 & 49-51 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. **This rejection is maintained for reasons of record in the office actions mailed 2/26/2003 & 12/16/2003, which grounds are repeated below.**

Each of the claims is directed towards an isolated protein having at least 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the polypeptide shown in Figure 90 (SEQ ID NO: 255 or PRO302). In addition, or alternatively, the rejected claims read on a protein having 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to SEQ ID NO: 255, but lacking its associated signal peptide. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255, but lacking the associated signal peptide. In addition, the isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the protein encoded by the coding sequence of ATCC deposit number 209485. The isolated protein can be a chimeric protein comprising the polypeptide of the invention fused to a heterologous peptide sequence (e.g. an epitope tag or an Fc region of an immunoglobulin.

SEQ ID NO: 255 appears to have been novel in the art at the time of filing. Likewise, the nucleic acid sequence disclosed by applicants as encoding SEQ ID NO: 255, SEQ ID NO: 254, likewise appears to be novel in the art. Therefore, there is no well-established utility for the claimed proteins.

The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro

utilities. There is no indication in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate).

It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone. Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one

cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess.

The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability. It is further noted that the observed activity is not unique to PRO302 in that at least one other protein and the positive control both induced vascular permeability in the guinea pig model. Based on these teachings, one of skill in the art at the time of applicants' invention would not be able to recognize a specific utility (e.g. specific proteolytic substrate) or substantial utility (i.e. not requiring additional research in order to confirm a real-world application for the claimed proteins) for the claimed proteins.

Claims 42-46 & 49-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following enablement rejection is provided in the event that the rejection outlined above under 35 U.S.C. 101 for lack of a specific and substantial or well-established utility is overcome. While it may be possible that applicants can demonstrate that the instant specification and/or prior art provides a specific and substantial or well-established utility for the claimed proteins, there remain other grounds for rejecting the instant claims under 35 U.S.C. 112 1st for lack of enablement. These additional grounds are outlined below.

Claims 42-46 & 49-51 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office actions mailed 2/26/2003 & 12/16/2003, which grounds are repeated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving the use of proteins without a well-defined function.

Breadth of the claims: The complexity of the invention is exacerbated by the great breadth of the claims, encompassing proteins with as little as 80% identity to SEQ ID NO: 255, or portions thereof (e.g. a purported extracellular domain). This includes a very large number of proteins that do not possess the specific activity of PRO302 and for which the specification provides no teachings as to a real-world use.

Guidance of the specification: The specification teaches that the cDNA encoding PRO302 was obtained from a human fetal kidney RNA library that was probed with oligomers designed from a putative extracellular domain for a given protein (e.g. Example 1, Example 85). The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Nor is it taught what exactly are the functional domains within the PRO302 polypeptide. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro utilities. There is no teaching in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate). The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to

envision a specific, real-world application for the asserted ability to induce vascular permeability.

The existence of working examples: The only working example for PRO302 is the experiment wherein it was purportedly shown that PRO302 can induce some unspecified degree of vascular permeability in the guinea pig.

State of the art/Predictability of the art: It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone.

Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires

extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess. Therefore, determining how to use the claimed polypeptides, even those having the same activity as determined for the protein described by SEQ ID NO: 255 would have been unpredictable at the time of filing.

The amount of experimentation necessary: Given the combination of factors outlined above, it would have required undue, unpredictable experimentation for one of skill in the art to use the claimed polypeptides. For example, in order to determine whether the a polypeptide meeting the claim limitations of a given percent identity to SEQ ID NO: 255, or portions thereof, has a particular activity one would have to envision an appropriate assay and conditions for measuring the purported activity. With proteolytic activity, one of skill in the art would have to envision which possible substrate of all the possible protein substrates available and under which conditions would be likely to result in an observation of the supposed activity. One would then have to envision the appropriate reaction conditions for performing the assay (e.g. purified or unpurified protein, temperature, buffer conditions, possible co-factors, etc.). If unsuccessful in determining an activity for the claimed protein, which is likely given the combination of factors outlined above and the unpredictability of the art, one of skill in the art would then have to envision a change to the first assay conditions (e.g. different substrate, buffer composition, temperature, duration and/or completely different assay) and repeat the entire unpredictable

process. Thus, it would require undue, unpredictable experimentation for one of skill in the art to use the claimed proteins having a specified percent identity to PRO302 (SEQ ID NO: 255). Therefore, the instant specification is not considered to be enabling for the use of any of the claimed proteins.

Response to Arguments/Utility and Enablement

Applicant's arguments filed on 12/14/2004 have been fully considered but they are not persuasive. The response essentially argues: 1) the examiner acknowledges that the exhibits presented previously demonstrate that the injection of PRO302 protein intra-dermally in guinea pigs will cause some vascular leakage, 2) under the Utility guidelines a "specific" utility is particular to the subject matter claimed, 3) the requirement of "substantial utility" requires a "real world" use, but does not require that a reasonable use identified by applicant has to be "currently available" to the public in order to satisfy the utility requirements, 4) based on the positive results shown in the exhibits of record, applicants have asserted a specific and substantial role for PRO302 where vascular leakage occurs, and 5) applicants plan to file an opinion Declaration by Sherman Fong, PhD., an expert in the field of immunology with discussion on the vascular leakage assay and its use to identify molecules that induce leakage, the mechanism of vascular leakage/permeability, how the assay and its modifications have been used in the art, etc.

To the extent that applicants' arguments are a reiteration of previous arguments already of record, the responses to these arguments presented in the papers mailed 2/26/2003, 12/16/2003 & 3/16/2004 are incorporated herein by reference. It is noted that applicants do not

significantly address the grounds of rejection presented under 35 U.S.C. 112 1st paragraph concerning enablement. Applicants are reminded that overcoming the utility rejection will not necessarily result in removal of the enablement rejection. The grounds of rejection made under 35 U.S.C. 112 1st paragraph for enablement must be overcome as well. With regard to the proposed Declaration by Dr. Fong, the declaration has not been filed to date and the examiner cannot make any judgment as to its contents.

Claims 42-44 & 50-51 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 12/16/2003, which grounds are repeated below.**

Each of the rejected claims is directed to a protein comprising a specified percent identity (e.g. 80%, 85%, 90%, 95% and 99%) to SEQ ID NO: 255, where the protein must necessarily be capable of enhancing vascular permeability. The protein described by SEQ ID NO: 255 is 452 amino acids in length. Thus, the claims encompass a large number of sequence variants of the protein described by SEQ ID NO: 255 that must retain the ability to enhance vascular permeability in an organism.

There is no discussion in the prior art or instant specification concerning the domains or specific amino acid residues that are responsible for the vascular permeabilization activity recited in the rejected claims. Therefore, there is no basis for the skilled artisan to envision a sufficient

number of specific embodiments of the protein variants to describe the broadly claimed genus of such proteins that retain the ability to enhance vascular permeability in an organism.

Response to Arguments/Written Description

Applicant's arguments filed on 12/14/2004 have been fully considered but they are not persuasive. The response essentially argues: 1) claims 39-41 have been cancelled, 2) Example 14 of the guidelines clearly states that proteins variants meet the description requirements so long as (i) the procedures for making a given protein are known in the art, (ii) the specification provides assays for detecting the functional activity of the protein, and (iii) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence, 3) Applicants submit that the genus of polypeptide variants of SEQ ID NO: 255 with 95% identity to PRO302 and which further possess the functional activity of "enhancing vascular permeability" would encompass a genus that meets the requirements of 35 U.S.C. 112 1st paragraph.

To the extent that applicants' response reiterates arguments already of record, the examiner's response presented in the Advisory Action of 3/16/2004 is incorporated herein by reference. The written description guidelines are just that, guidelines. Each example from the guidelines is not meant to set an absolute standard for meeting the description requirement that can be stretched to fit every fact pattern for every application. For example, the instant claims recite variants of an ~450 amino acid protein that can vary by as much as 5% over the entire length of the protein, and which must retain the recited activity of enhancing vascular leakage. This encompasses a change of up to ~22 amino acid residues at any point in the polypeptide.

Given the fact that such changes include additions, deletions and substitutions with up to 19 different amino acids at any given residue, the number of variants encompassed by the claimed genus of variants is incalculable. The instant specification does not describe a single variant that retains the recited activity. Nor does the specification provide any guidance as to what residues or domains within the protein are required for the recited activity. Thus, the specification provides no basis for the skilled artisan to envision which proteins encompassed by the structural limitations of the claims necessarily meets the functional limitations. For these reasons, the skilled artisan could not have envisioned a sufficient number of protein variants of SEQ ID NO: 255 that meet the functional limitations of the claims to describe the broadly claimed genus.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
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ggl

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PRIMARY EXAMINER